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From the Editor's desk...

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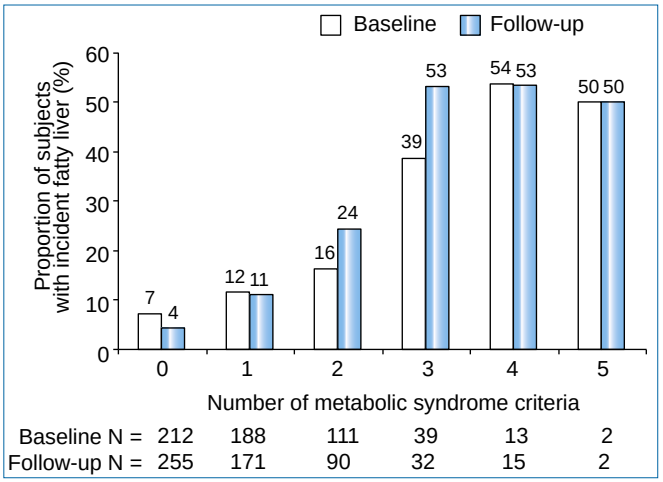
SELECTION OF THE MONTH

Alarming increase in NAFLD in China

Obesity is a growing health problem in Asian countries including China, where the obesity rate has doubled in the last 2 decades. As a consequence, the **incidence of NAFLD is rapidly rising**. Wong *et al.* performed a large prospective cohort study in Hong Kong, using state-of-the-art non-invasive methods. The incidence of NAFLD at 3-5 years was 13.5%, although few patients developed significant fibrosis. This important **study highlights the current burden of NAFLD in China** and also confirms previous data that liver fibrosis progresses slowly into fatty liver disease. While the incidence of NAFLD is growing, **there is an urgent need to develop specific therapies for patients with non-alcoholic steatohepatitis (NASH)** who are at a high risk of disease progression.



Wong et al., 2015

LIVER FIBROSIS

Intrahepatic myeloid cells, histone marks, and hepatic stellate cell activation

Two studies provide new insights into the mechanisms of **hepatic stellate cell (HSC) activation, which is a crucial event for the initiation of liver fibrosis**. Chen *et al.* show that the S100 calcium binding protein A4 **(S100A4) is produced by liver myeloid cells (mainly macrophages) and activates HSCs.** In patients with liver fibrosis, higher S100A4 levels in the liver and peripheral blood, correspond to a higher amount of fibrosis.

Tian *et al.* show in HSCs that the MKL/myocardin-like protein 1 (also known as **MRTF-A) recruits a histone methyltransferase complex to "fibrogenic" gene promoters** (analogue of the *S. cerevisiae* Set1/COMPASS complex) that induces di- and trimethylation of histone H3 at lysine 4 (H3K4me2 and H3K4me3, respectively). As these histone modifications are known to be associated with active genes, these studies identify targets for novel anti-fibrotic therapies.

LIVER CANCER

Role of protein kinases and accuracy of contrast-enhanced ultrasound

Three studies explore the link between inflammation or cell metabolism and hepatocellular carcinoma (HCC). Cubero *et al.* suggest that in animal models the gene *Mapk8* **(alias *Jnk1*), encoding a mitogen-activated Jun kinase, has a synergistic function in haematopoietic cells and hepatocytes, and is involved in the development of chronic liver injury and liver cancer.**

Zhang *et al.*, by investigating hepatitis B-related hepatocellular carcinomas bearing *p53* mutations, show that cases that exhibit evidence of **activation in both SIRT1 (a class III histone deacetylase) and AMP-activated protein kinase (AMPK) are associated with better outcomes** than those without SIRT1 and AMPK activation. Data are consistent with AMPK being located downstream of SIRT1 in the cascade of events. Beneficial effects of AMPK activation could be mediated by mTOR inhibition. Interestingly the fact that activation of AMPK with metformin "rescues" p53-deficient cell lines with inactive SIRT1 suggests that use of "personalized" metformin therapy should be evaluated in selected cases of HCC.

The study by Li *et al.* reveals that **autophagy is increased in "tumour-associated" neutrophils, resulting in sustained survival and pro-tumorigenic effects of these cells in human HCC.** These findings identify a new player (i.e., neutrophils) in the tumour environment as possible target for future therapies.

Forner *et al.* show that the **absence of contrast hyper-enhancement during the arterial phase at contrast-enhanced ultrasound (CEUS) in nodules <2 cm in a cirrhotic liver does not predict a less malignant profile.** They conclude that priority for the diagnostic work-up and treatment should not differ according to the contrast profile at CEUS.

NON-ALCOHOLIC LIVER DISEASE (NAFLD)

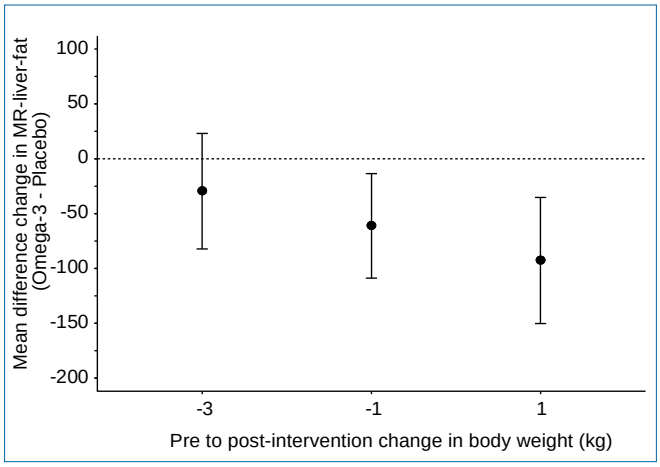
Epidemiology, N-3 polyunsaturated fatty acid replacement, and sortilin

Argo *et al.* investigated the histological and metabolic effects of n-3 polyunsaturated fatty acids (n-3 PUFAs), which are deficient in patients, and have been shown to have cardioprotective effects. Although N-3 PUFA supplementation did not improve histological features of NASH, it markedly reduced liver fat accumulation. These promising results suggest that **long-term dietary supplementation with polyunsaturated fatty acids may be beneficial**, and that a detailed nutritional assessment in patients with NASH may be part of patients' work-out in the future.

Despite these promising results, **more specific therapies that target key molecular drivers in NAFLD are warranted**.

The experimental study by Rabinowich *et al.* shed light on a **new potential player:**

sortilin. Sortilin traffics newly synthesized molecules from the Golgi apparatus and regulates ceramide levels by modulating acid sphingomyelinases.
Using a model of diet-induced NAFLD, the authors provide evidence that sortilin plays a role in the development of NAFLD by increasing ceramide production. This intriguing study suggests that proteins regulating ceramides could represent a potential target to treat fatty liver diseases.



Argo et al., 2015

VIRAL HEPATITIS

BE-LOW, HALT-C, cryoglobulinemia, and T cells

Dynamics of HBsAg levels during NUC treatment examined in the BE-LOW study by Zoulim *et al.* showed a strong correlation with HBeAg status, ALT levels and HBV genotype A. These findings may open the field for a more personalized treatment approach, in which timing of therapy may become an important issue.
The combination of telbivudine with pegylated interferon increases the overall antiviral efficacy but is also modifying the side effect profile of telbivudine. This is the lesson we learn from the study by Marcellin *et al.* evaluating the **safety and efficacy of telbivudine plus pegylated interferon alfa-2a in a randomized study.**
The so far largest evaluation of safety and efficacy of the **first generation protease inhibitor triple regimen for HCV-mixed cryoglobulinemic vasculitis** was performed by Saadoun *et al.*, demonstrating the potential benefits of the regimen but also emphasizing the risks for those with advanced fibrosis and low platelet counts.
A significant reduction in the risk of fibrosis progression among statin users with advanced chronic hepatitis C was described by Simon, King and co-workers by performing a post hoc analysis of the **HALT-C trial**. However, given the small number of statin users, the importance of the study is mainly due to paving the way for future studies, validating these findings.
By using new bioinformatics tools, Losikoff *et al.* describe a **unique viral peptide, derived from the HCV p7 protein that promotes an inhibitory Treg cell response** that cross-reacts with HLA-matched peptide sequences, located within hundreds of human proteins, hereby probably downregulating immune function and inducing HCV tolerance.
Reversing T cell exhaustion by targeting inhibitory co-regulatory molecules could provide a promising approach for restoring effective immunological control over persistent viral infections. However, highly variable inter-individual response patterns, observed by Sekyere and co-workers after antibody-mediated manipulation of the co-regulatory receptor signalling, will challenge its clinical development.

CIRRHOSIS

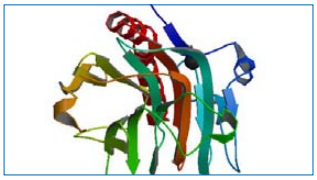
Brain function, inflammation, transplantation preconditioning and ischemia reperfusion injury

The complications of cirrhosis are the main reason for hospital admission and the occurrence of hepatic encephalopathy and infection/inflammation are important determinants of in-hospital mortality. The study of Ahluwalia *et al.* and the associated Editorial highlights that **treating hyponatraemia is more than just treating a result** and provides human evidence for the improvement of cognitive function and the reduction in brain oedema, following treatment of hyponatraemia.
The study by Lozano-Ruiz *et al.* provides novel evidence to suggest that the **inflammasome is highly activated in the ascitic fluid, mediated by the protein absent in melanoma 2 (AIM2)**, which has recently been described as the first non-NLR (nucleotide-binding domain leucine-rich repeat) receptor that induces inflammasome activation. This may have important implications in understanding the pathobiology of inflammation in liver failure.
The paper by Jiménez-Castro *et al.* describes important studies in rats, which show that the **addition of acetylcholine to the well-known protective effects of preconditioning may be highly protective** to improve graft function for organs obtained from brain dead donors. This study has the potential for clinical translation.
Important observations from Wang *et al.* provide further insights into the pathogenesis of hepatic ischemia reperfusion injury from studies in knock-out mice, which suggest that **interferon regulatory factor 9 (IRF-9) is a key regulator of ischemia reperfusion injury** and may well be a future target of therapy.
The study by Sharma and colleagues provides **important new insights into the role of hepatogenic microRNAs** in their ability to induce hepatocyte differentiation of embryonic stem cells. They identified an **important role for miR-199a-5p**. Its inhibition in human embryonic stem cell-derived hepatocyte-like cells increased the engraftment and repopulation capacity in immunodeficient mice. The data suggest that mIR modulation is an important target to generate more mature hepatocyte-like cells from embryonic stem cells.
Lluis-Castells *et al.* provide important **new data for therapy of post-transplant HIV/HCV co-infected patients with interferon and ribavirin.** They make the important observation of a **significantly lower virological response in co-infected patients (21%)** compared with mono-infected patients (36%; p = 0.01). However, patients that responded had excellent survival. These data justify trials of the new direct-acting antiviral drugs in this population.

SPLANCHNIC VEIN THROMBOSIS

A new mutation

A study by García-Pagán and colleagues describes that in patients with portal vein thrombosis or Budd-Chiari syndrome, **5.4% of patients with myeloproliferative diseases that are negative for the common *JAK2* mutation carry somatic mutations in the calreticulin (*CALR*) gene** (encoding a protein specific for the endoplasmic reticulum). They emphasize that a stepwise assessment may improve the diagnostic yield of myeloproliferative diseases and reduce the need for other diagnostic studies.



Ribbon diagram of calreticulin (RCSB Protein Data Bank)

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